Rejection Under 35 U.S.C. § 103

Claims 82-86, 91, 92, 97-104, and 109-132 were rejected under 35 U.S.C. § 103(a) as obvious over WO 92/19747 ("Bright"), Hayashi et al. *Transport of chimeric proteins that contain a carboxy-terminal targeting signal into plant microbodies*, The Plant Cell, 38(6): 759-768 (1997) ("Hayashi"), in view of Hahn et al., *Peroxisomal Localization of PHA Synthesis in Eukaryotic Cells*, International Symposium on Bacterial Polydydroxyalkanoates '96, (abstract and poster) 16 pgs. (1996) ("Hahn"), further in view of U.S. Patent 5,801,026 to Somerville et al. ("Somerville"), U.S. Patent RE37,317 to Hitz ("Hitz"), Elgersma et al. JBC 271, 42, p. 26375-26382 (1997) ("Elgersma"), Verleur et al. Eur. J. Biochem. 247, 972-980 (1997) ("Verleur"), U.S. Patent 6,146,847 to Gengenbach et al. ("Gengenbach"), U.S. Patent 6,258,999 to Tomes et al. ("Tomes"), and U.S. Patent 6,175,061 B1 to Bright et al. ("Bright2"). Applicants respectfully traverse these rejections.

Please note that the office action indicates that a copy of the Hahn reference would be faxed. No copy has been received to date, despite calls to the Examiner on December 26, 2001, and again on January 15, 2002, in which the examiner had stated that the office action would be remailed if she did not locate the reference, a copy not being available. Since the deadline to respond is no longer extendible, this response is being filed, however, it is believed the office action is now improper and at a minimum, a final rejection should not be issued if the claims are not deemed to be allowable.

The claimed invention

The invention defined by the claims is based on the discovery that PHA production can be targeted to peroxisomes, where there is a great concentration of substrate for production of the polymers, by targeting the enzymes required for production of the PHAs to the peroxisomes. This is achieved by construction of fusion nucleic acids, which encode the targeting sequence as well as the enzyme, so that when the enzyme is expressed in the host cell, the enzyme is transported into the peroxisome (see claims 82-90). Therefore, the peroxisome must supply the appropriate substrate for PHA production. The enzymes leading to PHA production have specific substrates to which they bind and catalyze their formation into a product that will be specifically utilized by the next gene encoded enzyme in the pathway. Enzymes dedicated to PHA synthesis are functioning in a specific and coordinated pathway, resembling a multi-step processing unit. This is the subject of claims 91-108. The method of preparing the cells is defined by claims 109-120. The method of making the PHAs using the cells is defined by claims 121-132. The priority date for this application is January 5, 1998.

The prior art

As noted above, Hahn is not available as a reference.

Bright (both the patent as well as the PCT application) disclose localization of enzymes for PHA production in the plastids of plants (col. 3, lines 55 to col. 4, line 36). There is no disclosure of targeting to peroxisomes, much less an enabling disclosure of how one could achieve targeting of the enzymes to the peroxisomes, nor any expectation that the enzymes if

targeted would be active and polymer produced.

Somerville *et al.*, is the same as Bright. There is a general disclosure of targeting to plastids, but nothing with respect to peroxisomes.

As the examiner has noted, Elgersma, et al., describes targeting of a single enzyme, not involved in PHA production, to the peroxisome. There is no teaching that peroxisomes would contain appropriate substrate for PHA production, nor any teaching that would lead one to believe that there could be the coordinated enzymatic processing of substrate required to yield polymer, since neither reference discloses anything other than a single enzyme, active on a single substrate. Even in this regard, Hayashi measures only protein transport, not enzymatic activity.

Verleur, et al., appears to be looking at an endogenous peroxisome enzyme, not one that is created with a targeting sequence for transport into the peroxisome.

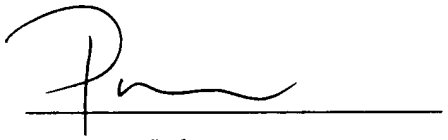
The undersigned agrees with the comments regarding Hitz, Gengenbach, et al., and Tomes.

None of the prior art, alone or in combination, teaches one to target enzymes involved in PHA production to the peroxisome, much less that one would have a reasonable expectation of success if one did so. Additionally, except in hindsight based on the applicant's disclosure, there is no suggestion to one of ordinary skill in the art to combine the cited references and derive applicant's claimed methods and compositions. The processing of substrate in the pathway leading to PHA synthesis is coordinately regulated. This coordinated activity relies upon the presence of substrate. The Applicants have shown that by increasing the specific substrates

required for PHA synthesis, via fatty acid processing in the peroxisomal beta-oxidation cycle, increased PHA end product is observed when peroxisomally localized enzymatic activity is present. None of the cited prior art shows 1) that appropriate substrates for PHA synthesis exist in the peroxisome, 2) how one would obtain enough appropriate substrate to produce PHAs, or 3) how PHA synthesis is compartmentalized within a recombinant cell via the localization of substrate and the localization of coordinated enzymatic activity to the peroxisome. Again, the enzymes leading to PHA production have specific substrates to which they bind and catalyze their formation into a product that will be specifically utilized by the next gene encoded enzyme in the pathway. Enzymes dedicated to PHA synthesis are functioning in a specific and coordinated pathway therefore resembling a multi-step processing unit. None of the prior art, alone or in combination, provides motivation to localize enzymes to the peroxisome, specifically for the purpose of PHA synthesis, because such localization would not provide for a PHA end product without the proper substrate feeding into the pathway. Without knowledge of the proper substrate present in the peroxisome, there would not be a reasonable expectation of success for the production of PHA. Furthermore, the localization of a single enzyme would only serve to process a single substrate (if it is present). As mentioned in the foregoing discussion, PHA synthesis relies upon a "chain" of enzymatic activities with each enzyme link in the chain processing the substrate produced from the previous enzymatic link. This coordinated enzymatic processing results in polymer. Accordingly, the prior art does not meet the legal standard under 35 USC 103 for making obvious the claimed subject matter.

Allowance of claims 82-133 is therefore earnestly solicited.

Respectfully submitted,



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Date: February 28, 2002

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I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Jean Hicks

Date: February 28, 2002